Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	65048	(|435/4|435/6|435/72.3|435/320.1|435/325|536/23.2|.ccls.)	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/10/05 08:48
L2	63	l1 and mre11	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/10/05 08:50
L3	131	l1 and hitoshi.in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/10/05 08:50
L4	1	l3 and mre11	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/10/05 08:50
L5	579	l1 and young.in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/10/05 08:50
L6	0	l5 and mre11	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/10/05 08:50
L7	0	l5 and morris.in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/10/05 08:51
L8	157	l1 and morris.in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/10/05 08:51
L9	0	l8 and mre11	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/10/05 08:51
L10	5	mre-11	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/10/05 08:51
L11	113	mre11	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/10/05 08:51
L12	0	l11 and morris.in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/10/05 08:53

L13	44301	young.in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/10/05 08:53
L14	1	l13 and "cancer gene sets"	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/10/05 08:54
L15	0	l14 and mre11	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/10/05 08:54
L16	0	l14 and "DNA repair"	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/10/05 08:54
L17	32	morris.in. and engelhard.in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/10/05 08:54
L18	0	l17 and mre11	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/10/05 09:09
L19	289	bevilacqua.in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/10/05 09:09
L20	1	l19 and mre11	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/10/05 09:10
L21	0	"6692916".in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/10/05 09:10
L22	116597	hitoshi.in. or demo.in. or jenkins. in. or rigel$.as.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2005/10/05 09:19
L23	225	l22 and l1	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2005/10/05 09:19
L24	1	l23 and mre11	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2005/10/05 09:19

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	65048	(|435/4|435/6|435/72.3|435/320.1|435/325|536/23.2|.ccls.)	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/10/05 08:48
L2	63	l1 and mre11	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/10/05 08:50
L3	131	l1 and hitoshi.in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/10/05 08:50
L4	1	l3 and mre11	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/10/05 08:50
L5	579	l1 and young.in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/10/05 08:50
L6	0	l5 and mre11	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/10/05 08:50
L7	0	l5 and morris.in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/10/05 08:51
L8	157	l1 and morris.in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/10/05 08:51
L9	0	l8 and mre11	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/10/05 08:51
L10	5	mre-11	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/10/05 08:51
L11	113	mre11	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/10/05 08:51
L12	0	l11 and morris.in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/10/05 08:53

L13	44301	young.in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/10/05 08:53
L14	1	l13 and "cancer gene sets"	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/10/05 08:54
L15	0	l14 and mre11	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/10/05 08:54
L16	0	l14 and "DNA repair"	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/10/05 08:54
L17	32	morris.in. and engelhard.in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/10/05 08:54
L18	0	l17 and mre11	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/10/05 09:09
L19	289	bevilacqua.in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/10/05 09:09
L20	1	l19 and mre11	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/10/05 09:10
L21	0	"6692916".in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/10/05 09:10
L22	116597	hitoshi.in. or demo.in. or jenkins. in. or rigel$.as.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2005/10/05 09:19
L23	225	l22 and l1	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2005/10/05 09:19
L24	1	l23 and mre11	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2005/10/05 09:19

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	116597	hitoshi.in. or demo.in. or jenkins. in. or rigel$.as.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2005/10/04 17:31
L2	121	MRE11 or ((meiotic near2 recombination) near2 "11")	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2005/10/04 17:32
L3	2	l1 and l2	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2005/10/04 17:33
L4	50435	cell near2 proliferation	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2005/10/04 17:34
L5	56	cell near2 chemosensitivity	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2005/10/04 17:34
L6	39	l2 and l4	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2005/10/04 17:34
L7	39	l2 and l6	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2005/10/04 17:34
L8	49188	(screening or screen or assay) with compound	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2005/10/04 17:35
L9	15	l6 and l8	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2005/10/04 17:35
L10	87179	"drug screen" or "therapeutic agent"	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/10/04 18:36
L11	3	NBS1 WITH RAD	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/10/04 18:36
L12	20883	engelhard.in. or morris.in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/10/04 18:37

L13	39777	PC3 or HI299 or MDA or MB-231 or MCF7 or A549 or hela	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/10/04 18:37
L14	495077	(system or method or process) WITH (identification or identifying or isolation or isolating)	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/10/04 18:37
L15	42	l10 and l2	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2005/10/04 18:38
L16	45	l13 and l2	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2005/10/04 18:38
L17	1	l16 and l1	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2005/10/04 18:39
L18	0	l16 and l12	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2005/10/04 18:38
L19	27	l4 and l5	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2005/10/04 18:39
L20	0	l19 and l1	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2005/10/04 18:40
L21	35	l8 and l2	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2005/10/04 18:40
L22	0	l21 and l1	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2005/10/04 18:40
L23	0	l21 and l12	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2005/10/04 18:40
L24	23	l21 and l10	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2005/10/04 18:41

L25	10	l24 and l13	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2005/10/04 18:40

	Document ID	Title
16	US 20030188326 A1	Methods and compositions for the diagnosis of cancer susceptibilities and defective DNA repair mechanisms and treatment thereof
17	US 20030022263 A1	ATM kinase modulation for screening and therapies
18	US 6747137 B1	Nucleic acid sequences relating to Candida albicans for diagnostics and therapeutics
19	US 6692916 B2	Systems and methods for characterizing a biological condition or agent using precision gene expression profiles
20	US 6387640 B1	ATM kinase modulation for screening and therapies
21	US 6348311 B1	ATM kinase modulation for screening and therapies
22	US 6057104 A	Disruption of the mammalian Rad51 protein and disruption of proteins that associate with mammalian Rad51 for hindering cell proliferation
23	US 6037125 A	Disruption of the mammalian RAD51 protein and disruption of proteins that associate with mammalian RAD51 for hindering cell proliferation and/or viability of proliferating cells

	Document ID	Title
9	US 20040110227 A1	Methods and systems for identifying putative fusion transcripts, polypeptides encoded therefrom and polynucleotide sequences related thereto and methods and kits utilizing same
10	US 20040097446 A1	Modulation of checkpoint kinase 1 expression
11	US 20040091926 A1	Compositions, organisms and methodologies employing a novel human protein phosphatase
12	US 20040077090 A1	Whole cell engineering by mutagenizing a substantial portion of a starting genome, combining mutations, and optionally repeating
13	US 20040038207 A1	Gene expression in bladder tumors
14	US 20040023235 A1	Methods for detecting dna damage and screening for cancer therapeutics
15	US 20030207451 A1	Methods, compositions, and kits for enhancing oligonucleotide-mediated nucleic acid sequence alteration using compositions comprising a histone deacetylase inhibitor, lambda phage beta protein, or hydroxyurea

	Document ID	Title
1	US 20040225449 A1	Systems and methods for characterizing a biological condition or agent using selected gene expression profiles
2	US 20040225448 A1	Systems and methods for characterizing a biological condition or agent using selected gene expression profiles
3	US 20040225447 A1	Systems and methods for characterizing a biological condition or agent using selected gene expression profiles
4	US 20040225446 A1	Systems and methods for characterizing a biological condition or agent using selected gene expression profiles
5	US 20040225445 A1	Systems and methods for characterizing a biological condition or agent using selected gene expression profiles
6	US 20040224333 A1	Systems and methods for characterizing a biological condition or agent using selected gene expression profiles
7	US 20040224322 A1	Systems and methods for characterizing a biological condition or agent using selected gene expression profiles
8	US 20040219568 A1	Systems and methods for characterizing a biological conditions or agent using selected gene expression profiles

	Document ID	Title
8	US 20030207451 A1	Methods, compositions, and kits for enhancing oligonucleotide-mediated nucleic acid sequence alteration using compositions comprising a histone deacetylase inhibitor, lambda phage beta protein, or hydroxyurea
9	US 20030188326 A1	Methods and compositions for the diagnosis of cancer susceptibilities and defective DNA repair mechanisms and treatment thereof
10	US 6747137 B1	Nucleic acid sequences relating to Candida albicans for diagnostics and therapeutics

	Document ID	Title
1	US 20040225449 A1	Systems and methods for characterizing a biological condition or agent using selected gene expression profiles
2	US 20040110227 A1	Methods and systems for identifying putative fusion transcripts, polypeptides encoded therefrom and polynucleotide sequences related thereto and methods and kits utilizing same
3	US 20040097446 A1	Modulation of checkpoint kinase 1 expression
4	US 20040091926 A1	Compositions, organisms and methodologies employing a novel human protein phosphatase
5	US 20040077090 A1	Whole cell engineering by mutagenizing a substantial portion of a starting genome, combining mutations, and optionally repeating
6	US 20040038207 A1	Gene expression in bladder tumors
7	US 20040023235 A1	Methods for detecting dna damage and screening for cancer therapeutics

	Document ID	Title
1	US 20030027167 A1	MRE11: modulation of cellular proliferation

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	65048	(|435/4|435/6|435/72.3|435/320.1|435/325|536/23.2|.ccls.)	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/10/05 08:48
L2	63	l1 and mre11	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/10/05 08:50
L3	131	l1 and hitoshi.in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/10/05 08:50
L4	1	l3 and mre11	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/10/05 08:50
L5	579	l1 and young.in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/10/05 08:50
L6	0	l5 and mre11	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/10/05 08:50
L7	0	l5 and morris.in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/10/05 08:51
L8	157	l1 and morris.in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/10/05 08:51
L9	0	l8 and mre11	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/10/05 08:51
L10	5	mre-11	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/10/05 08:51
L11	113	mre11	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/10/05 08:51
L12	0	l11 and morris.in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/10/05 08:53

L13	44301	young.in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/10/05 08:53
L14	1	l13 and "cancer gene sets"	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/10/05 08:54
L15	0	l14 and mre11	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/10/05 08:54
L16	0	l14 and "DNA repair"	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/10/05 08:54
L17	32	morris.in. and engelhard.in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/10/05 08:54
L18	0	l17 and mre11	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/10/05 08:54

```
  FILE 'MEDLINE, EMBASE, BIOSIS' ENTERED AT 13:42:05 ON 05 OCT 2005
L1         53343 S CHEMOTHERAPEUTIC
L2             3 S L1 AND MRE11
L3             1 DUP REM L2 (2 DUPLICATES REMOVED)
L4             0 S EFFECT (2W) MRE11
L5           158 S DSBR
L6             3 S L5 AND MRE11
L7             1 DUP REM L6 (2 DUPLICATES REMOVED)
L8            24 S SCREEN (P) MRE11
L9             9 DUP REM L8 (15 DUPLICATES REMOVED)
L10            5 S L9 NOT PY>=2002
L11            3 S L9 NOT PY<=2002
L12        52137 S BLEOMYCIN
L13         1798 S L12 AND "DNA DAMAGE"
L14           65 S L13 AND PROLIFERATION
L15            0 S L14 AND MRE11
L16           41 S L14 NOT PY>=2002
L17           38 S L16 AND CELL
L18            6 S L17 AND REPAIR
L19       165500 S PC3 OR HI299 OR MDA OR MCF7 OR A549 OR HELA
L20         2978 S L19 (S) PROLIFERATION
L21            1 S L20 AND "DOUBLE STRAND BREAK"
L22           28 S L20 AND REPAIR
L23           15 DUP REM L22 (13 DUPLICATES REMOVED)
L24            3 S L23 AND (TELOMERE OR RECOMBINATION OR REPLICATION OR MITOSIS
```

```
 FILE 'MEDLINE, EMBASE, BIOSIS' ENTERED AT 11:57:32 ON 05 OCT 2005
L1       274647 S HITOSHI?/AU OR JENKINS?/AU OR DEMO?/AU OR YOUNG?/AU OR MORRIS
L2         1202 S MRE11
L3          105 S (SCREENING OR ASSAY OR SCREEN OR ASSAYING) (P) L2
L4            0 S L3 AND L1
L5       103779 S (LIGAND OR SUBSTRATE) (2W) BIND?
L6            0 S L5 AND L3
L7            0 S L5 AND L2
L8           38 S ANTIBODY AND L2
L9            5 S L8 AND L3
L10           3 DUP REM L9 (2 DUPLICATES REMOVED)
L11      142610 S DNA (2W) SYNTHESIS
L12          65 S L11 AND L2
L13          25 S L12 NOT PY>=2002
L14          10 DUP REM L13 (15 DUPLICATES REMOVED)
L15         443 S L2 (2W) (PROTEIN OR PEPTIDE)
L16          38 S L15 AND L3
L17          13 S L16 NOT PY>=2002
L18           9 DUP REM L17 (4 DUPLICATES REMOVED)
L19         892 F JOD
L20           0 S L1 AND L2 AND L3
L21          28 S L1 AND L2
L22          19 S L21 NOT PY>=2002
L23           7 DUP REM L22 (12 DUPLICATES REMOVED)
L24         294 S (ANTISENSE OR "SMALL MOLECULE" OR DRUG OR ANTIBODY) AND L2
L25          12 S L24 AND PROLIFERATION
L26          12 DUP REM L25 (0 DUPLICATES REMOVED)
L27           1 S L26 NOT PY>=2002
L28           3 S RECOMBINANT (3W) L2
L29           1 DUP REM L28 (2 DUPLICATES REMOVED)
L30         746 S (TRANSFORMED (2W) CELL) AND (HELA OR PC3 OR HI299 OR MDA OR M
L31           0 S L30 AND L2
L32         106 S P53 AND L2
L33          21 S L32 NOT PY>=2002
L34          10 DUP REM L33 (11 DUPLICATES REMOVED)
```

L18 ANSWER 2 OF 6 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2001340707 EMBASE

TITLE: Visualization of focal nuclear sites of DNA **repair** synthesis induced by **bleomycin** in human cells.

AUTHOR: Tomilin N.V.; Solovjeva L.V.; Svetlova M.P.; Pleskach N.M.; Zalenskaya I.A.; Yau P.M.; Bradbury E.M.

CORPORATE SOURCE: N.V. Tomilin, Institute of Cytology RAS, Tikchoretskii Av. 4, 194064 St. Petersburg, Russian Federation. nvtom@mail.ru

SOURCE: Radiation Research, (2001) Vol. 156, No. 4, pp. 347-354.
Refs: 44
ISSN: 0033-7587 CODEN: RAREAE

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 022 Human Genetics
029 Clinical Biochemistry
037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 20011018
Last Updated on STN: 20011018

AB In this study, we examined DNA **repair** synthesis in human cells treated with the radiomimetic drug **bleomycin**, which efficiently induces double-strand breaks (DSBs). Using tyramide-biotin to amplify fluorescent signals, discrete nuclear foci from the incorporation of 5-iododeoxyuridine (IdU) were detected in proliferating human cells treated with **bleomycin**. We believe this comes from the **repair** of DSBs. An increase in the number of foci (> 5 per nucleus) was detected in a major fraction (75%) of non-S-phase cells labeled for 30 min with IdU 1 h after the end of **bleomycin** treatment. The fraction of cells with multiple IdU-containing foci was found to decrease 18 h after treatment. The average number of foci per nucleus detected 1 h after **bleomycin** treatment was found to decrease twofold between 1 and 3.5 h, indicating that the foci may be associated with the slow component of DSB **repair**. The presence of DSBs in **bleomycin**-treated cells was confirmed using antibodies against phosphorylated histone H2AX (γ-H2AX), which is strictly associated with this type of **DNA damage**. After treatment with **bleomycin**, non-S-phase cells also displayed heterogeneous nuclear foci containing tightly bound proliferating **cell** nuclear antigen (PCNA), suggesting an ongoing process of unscheduled DNA synthesis. PCNA is known to be involved in base excision **repair**, but a fraction of the PCNA foci may also be associated with DNA synthesis occurring during the **repair** of DSBs.

enhanced in transformed XPV cells, indicating the activation of a recombination pathway. We now have identified that XPV cells make use of a homologous recombination pathway involving the hMre11/hRad50/Nbs1 protein complex, but not the Rad51 recombination pathway. The hMre11 complexes form at arrested replication forks, in association with proliferating cell nuclear antigen. In x-ray-damaged cells, in contrast, there is no association between hMre11 and proliferating cell nuclear antigen. This recombination pathway assumes greater importance in transformed XPV cells that lack a functional **p53** pathway and can be detected at lower frequencies in excision-defective XPA fibroblasts and normal cells. DNA replication arrest after UV damage, and the associated S phase checkpoint, is therefore a complex process that can recruit a recombination pathway that has a primary role in repair of double-strand breaks from x-rays. The symptoms of elevated solar carcinogenesis in XPV patients therefore may be associated with increased genomic rearrangements that result from double-strand breakage and rejoining in cells of the skin in which **p53** is inactivated by UV-induced mutations.

L34 ANSWER 5 OF 10 MEDLINE on STN DUPLICATE 3

ACCESSION NUMBER: 2000474246 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10908350
TITLE: The **MRE11**-NBS1-RAD50 pathway is perturbed in SV40 large T antigen-immortalized AT-1, AT-2 and HL-1 cardiomyocytes.
AUTHOR: Lanson N A Jr; Egeland D B; Royals B A; Claycomb W C
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, Louisiana State University Health Sciences Center, New Orleans, LA 70112, USA.
CONTRACT NUMBER: HL59879 (NHLBI)
SOURCE: Nucleic acids research, (2000 Aug 1) 28 (15) 2882-92. Journal code: 0411011. ISSN: 1362-4962.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AF218574; GENBANK-AF218575; GENBANK-AF218576
ENTRY MONTH: 200010
ENTRY DATE: Entered STN: 20001012
Last Updated on STN: 20030218
Entered Medline: 20001005

AB To investigate molecular controls of cardiomyocyte proliferation, we utilized cardiomyocytes induced to proliferate indefinitely by SV40 large T antigen (T-ag). In the T-ag-immortalized AT-1, AT-2 and HL-1 cardiomyocytes, normal cellular proteins associating with T-ag and **p53** were identified, isolated and micro-sequenced. Peptide sequencing revealed that proteins of 90, 100 and 160 kDa were homologs of **MRE11**, NBS1 and RAD50, respectively. These three proteins play critical roles in the detection and repair of DNA double-strand breaks, activation of cell cycle checkpoints and telomere maintenance. In this report, we describe the cDNA cloning and double-strand sequencing of the rat homologs of **MRE11**, NBS1 and RAD50. We also determined the mRNA and protein levels of **MRE11**, NBS1 and RAD50 at different stages of heart development and in different tissues. **MRE11** mRNA was only detected in the immortalized cardiomyocytes and in the testes. Although the 90 kDa **MRE11** protein was seen in most samples examined, it was only detected at extremely low levels in proliferating cardiomyocytes (normal and immortalized). The 6.0 kb **MRE11**-related mRNA transcript (MRT) was seen in all samples examined. Levels of both NBS1 and RAD50 mRNA transcripts peaked in the heart at postnatal day 10. NBS1 mRNA levels were at very low levels in the T-ag-immortalized AT-1, AT-2 and HL-1 cells but NBS1 protein was observed at extremely high levels. We propose that SV40 large T antigen's interaction with the **MRE11**-NBS1-RAD50 pathway and with **p53** ablates critical cell cycle checkpoints and that this is one of the major factors involved in the ability of this oncoprotein to immortalize cardiomyocytes.

L34 ANSWER 6 OF 10 MEDLINE on STN DUPLICATE 4

ACCESSION NUMBER: 2001108369 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11134068
TITLE: **p53** binding protein 1 (53BP1) is an early participant in the cellular response to DNA double-strand breaks.
AUTHOR: Schultz L B; Chehab N H; Malikzay A; Halazonetis T D
CORPORATE SOURCE: Department of Molecular Genetics, The Wistar Institute, Philadelphia, Pennsylvania 19104, USA.
CONTRACT NUMBER: CA76367 (NCI)
SOURCE: Journal of cell biology, (2000 Dec 25) 151 (7) 1381-90. Journal code: 0375356. ISSN: 0021-9525.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200102
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20020725
Entered Medline: 20010208

AB **p53** binding protein 1 (53BP1), a protein proposed to function as a transcriptional coactivator of the **p53** tumor suppressor, has BRCT domains with high homology to the Saccharomyces cerevisiae Rad9p DNA damage checkpoint protein. To examine whether 53BP1 has a role in the cellular response to DNA damage, we probed its intracellular localization by immunofluorescence. In untreated primary cells and U2OS osteosarcoma cells, 53BP1 exhibited diffuse nuclear staining; whereas, within 5-15 min after exposure to ionizing radiation (IR), 53BP1 localized at discreet nuclear foci. We propose that these foci represent sites of processing of DNA double-strand breaks (DSBs), because they were induced by IR and chemicals that cause DSBs, but not by ultraviolet light; their peak number approximated the number of DSBs induced by IR and decreased over time with kinetics that parallel the rate of DNA repair; and they colocalized with IR-induced **Mre11**/NBS and gamma-H2AX foci, which have been previously shown to localize at sites of DSBs. Formation of 53BP1 foci after irradiation was not dependent on ataxia-telangiectasia mutated (ATM), Nijmegen breakage syndrome (NBS1), or wild-type **p53**. Thus, the fast kinetics of 53BP1 focus formation after irradiation and the lack of dependency on ATM and NBS1 suggest that 53BP1 functions early in the cellular response to DNA DSBs.

L34 ANSWER 7 OF 10 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2001:60931 BIOSIS
DOCUMENT NUMBER: PREV200100060931
TITLE: The potential role of **p53** in DNA double-strand break rejoining.
AUTHOR(S): Bristow, R. [Reprint author]; Jalali, F. [Reprint author]; Al-Rashid, S. [Reprint author]
CORPORATE SOURCE: Ontario Cancer Institute-Princess Margaret Hospital-UHN, Departments of Radiation Oncology and Medical Biophysics, University of Toronto, Toronto, Canada
SOURCE: Radiotherapy and Oncology, (September, 2000) Vol. 56, No. Supplement 1, pp. S53-S54. print.
Meeting Info.: 19th Annual Meeting of the European Society for Therapeutic Radiology and Oncology. Istanbul, Turkey. September 19-23, 2000. European Society for Therapeutic Radiology and Oncology.
CODEN: RAONDT. ISSN: 0167-8140.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 31 Jan 2001
Last Updated on STN: 12 Feb 2002

L34 ANSWER 8 OF 10 MEDLINE on STN DUPLICATE 5
ACCESSION NUMBER: 2000076412 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10608806
TITLE: Substrate specificities and identification of putative substrates of ATM kinase family members.

AUTHOR: Kim S T; Lim D S; Canman C E; Kastan M B
CORPORATE SOURCE: Department of Hematology, St. Jude Children's Research Hospital, Memphis, Tennessee 38105, USA.
CONTRACT NUMBER: CA21765 (NCI)
CA71387 (NCI)
ES0577 (NIEHS)
SOURCE: Journal of biological chemistry, (1999 Dec 31) 274 (53) 37538-43.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200002
ENTRY DATE: Entered STN: 20000218
Last Updated on STN: 20020420
Entered Medline: 20000208

AB Ataxia telangiectasia mutated (ATM) phosphorylates **p53** protein in response to ionizing radiation, but the complex phenotype of AT cells suggests that it must have other cellular substrates as well. To identify substrates for ATM and the related kinases ATR and DNA-PK, we optimized in vitro kinase assays and developed a rapid peptide screening method to determine general phosphorylation consensus sequences. ATM and ATR require Mn(2+), but not DNA ends or Ku proteins, for optimal in vitro activity while DNA-PKCs requires Mg(2+), DNA ends, and Ku proteins. From **p53** peptide mutagenesis analysis, we found that the sequence S/TQ is a minimal essential requirement for all three kinases. In addition, hydrophobic amino acids and negatively charged amino acids immediately NH(2)-terminal to serine or threonine are positive determinants and positively charged amino acids in the region are negative determinants for substrate phosphorylation. We determined a general phosphorylation consensus sequence for ATM and identified putative in vitro targets by using glutathione S-transferase peptides as substrates. Putative ATM in vitro targets include p95/nibrin, **Mre11**, Brca1, Rad17, PTS, WRN, and ATM (S440) itself. Brca2, phosphatidylinositol 3-kinase, and DNA-5B peptides were phosphorylated specifically by ATR, and DNA Ligase IV is a specific in vitro substrate of DNA-PK.

L34 ANSWER 9 OF 10 MEDLINE on STN DUPLICATE 6
ACCESSION NUMBER: 2000094337 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10630641
TITLE: DNA damage-induced cell cycle checkpoints and DNA strand break repair in development and tumorigenesis.
AUTHOR: Dasika G K; Lin S C; Zhao S; Sung P; Tomkinson A; Lee E Y
CORPORATE SOURCE: Department of Molecular Medicine, Institute of Biotechnology, University of Texas Health Science Center at San Antonio, 78245, USA.
CONTRACT NUMBER: 1R01NS378381 (NINDS)
SOURCE: Oncogene, (1999 Dec 20) 18 (55) 7883-99. Ref: 202
Journal code: 8711562. ISSN: 0950-9232.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200001
ENTRY DATE: Entered STN: 20000131
Last Updated on STN: 20000131
Entered Medline: 20000120

AB Several newly identified tumor suppressor genes including ATM, NBS1, BRCA1 and BRCA2 are involved in DNA double-strand break repair (DSBR) and DNA damage-induced checkpoint activation. Many of the gene products involved in checkpoint control and DSBR have been studied in great detail in yeast. In addition to evolutionarily conserved proteins such as Chk1 and Chk2, studies in mammalian cells have identified novel proteins such as **p53** in executing checkpoint control. DSBR proteins including **Mre11**, Rad50, Rad51, Rad54, and Ku are present in yeast and in mammals. Many of the tumor suppressor gene products interact with these

repair proteins as well as checkpoint regulators, thus providing a biochemical explanation for the pleiotropic phenotypes of mutant cells. This review focuses on the proteins mediating G1/S, S, and G2/M checkpoint control in mammalian cells. In addition, mammalian DSBR proteins and their activities are discussed. An intricate network among DNA damage signal transducers, cell cycle regulators and the DSBR pathways is illustrated. Mouse knockout models for genes involved in these processes have provided valuable insights into their function, establishing genomic instability as a major contributing factor in tumorigenesis.

L34 ANSWER 10 OF 10 EMBASE

ACCESSION NUMBER: 2000257612 EMBASE

TITLE: The mammalian **Mre11**-Rad50,-Nbs1 protein complex: Integration of functions in the cellular DNA-damage response.

AUTHOR: Petrini J.H.J.

CORPORATE SOURCE: Dr. J.H.J. Petrini, Laboratory of Genetics, Univ. of Wisconsin Medical School, 445 Henry Mall, Madison, WI 53706, United States. jpetrini@facstaff.wisc.edu

SOURCE: American Journal of Human Genetics, (1999) Vol. 64, No. 5, pp. 1264-1269.
Refs: 33
ISSN: 0002-9297 CODEN: AJHGAG

COUNTRY: United States

DOCUMENT TYPE: Journal; General Review

FILE SEGMENT: 004 Microbiology
022 Human Genetics
029 Clinical Biochemistry

LANGUAGE: English

ENTRY DATE: Entered STN: 20000810
Last Updated on STN: 20000810

DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

=>

L34 ANSWER 1 OF 10 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2001384909 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11438675
TITLE: Chk2 activation dependence on Nbs1 after DNA damage.
AUTHOR: Buscemi G; Savio C; Zannini L; Micciche F; Masnada D; Nakanishi M; Tauchi H; Komatsu K; Mizutani S; Khanna K; Chen P; Concannon P; Chessa L; Delia D
CORPORATE SOURCE: Department of Experimental Oncology, Istituto Nazionale Tumori, 20133 Milan, Italy.
SOURCE: Molecular and cellular biology, (2001 Aug) 21 (15) 5214-22. Journal code: 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 20010820
Last Updated on STN: 20020725
Entered Medline: 20010816

AB The checkpoint kinase Chk2 has a key role in delaying cell cycle progression in response to DNA damage. Upon activation by low-dose ionizing radiation (IR), which occurs in an ataxia telangiectasia mutated (ATM)-dependent manner, Chk2 can phosphorylate the mitosis-inducing phosphatase Cdc25C on an inhibitory site, blocking entry into mitosis, and **p53** on a regulatory site, causing G(1) arrest. Here we show that the ATM-dependent activation of Chk2 by gamma- radiation requires Nbs1, the gene product involved in the Nijmegen breakage syndrome (NBS), a disorder that shares with AT a variety of phenotypic defects including chromosome fragility, radiosensitivity, and radioresistant DNA synthesis. Thus, whereas in normal cells Chk2 undergoes a time-dependent increased phosphorylation and induction of catalytic activity against Cdc25C, in NBS cells null for Nbs1 protein, Chk2 phosphorylation and activation are both defective. Importantly, these defects in NBS cells can be complemented by reintroduction of wild-type Nbs1, but neither by a carboxy-terminal deletion mutant of Nbs1 at amino acid 590, unable to form a complex with and to transport **Mre11** and Rad50 in the nucleus, nor by an Nbs1 mutated at Ser343 (S343A), the ATM phosphorylation site. Chk2 nuclear expression is unaffected in NBS cells, hence excluding a mislocalization as the cause of failed Chk2 activation in Nbs1-null cells. Interestingly, the impaired Chk2 function in NBS cells correlates with the inability, unlike normal cells, to stop entry into mitosis immediately after irradiation, a checkpoint abnormality that can be corrected by introduction of the wild-type but not the S343A mutant form of Nbs1. Altogether, these findings underscore the crucial role of a functional Nbs1 complex in Chk2 activation and suggest that checkpoint defects in NBS cells may result from the inability to activate Chk2.

L34 ANSWER 2 OF 10 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2001204624 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11238909
TITLE: Phosphorylation and rapid relocalization of 53BP1 to nuclear foci upon DNA damage.
AUTHOR: Anderson L; Henderson C; Adachi Y
CORPORATE SOURCE: The Wellcome Trust Centre for Cell Biology, Institute of Cell & Molecular Biology, University of Edinburgh, Edinburgh EH9 3JR, United Kingdom.
SOURCE: Molecular and cellular biology, (2001 Mar) 21 (5) 1719-29. Journal code: 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200104
ENTRY DATE: Entered STN: 20010417
Last Updated on STN: 20030218
Entered Medline: 20010412

AB 53BP1 is a human BRCT protein that was originally identified as a

p53-interacting protein by the Saccharomyces cerevisiae two-hybrid screen. Although the carboxyl-terminal BRCT domain shows similarity to Crb2, a DNA damage checkpoint protein in fission yeast, there is no evidence so far that implicates 53BP1 in the checkpoint. We have identified a Xenopus homologue of 53BP1 (XL53BP1). XL53BP1 is associated with chromatin and, in some cells, localized to a few large foci under normal conditions. Gamma-ray irradiation induces increased numbers of the nuclear foci in a dose-dependent manner. The damage-induced 53BP1 foci appear rapidly (in 30 min) after irradiation, and de novo protein synthesis is not required for this response. In human cells, 53BP1 foci colocalize with Mrel1 foci at later stages of the postirradiation period. XL53BP1 is hyperphosphorylated after X-ray irradiation, and inhibitors of ATM-related kinases delay the relocalization and reduce the phosphorylation of XL53BP1 in response to X-irradiation. In AT cells, which lack ATM kinase, the irradiation-induced responses of 53BP1 are similarly affected. These results suggest a role for 53BP1 in the DNA damage response and/or checkpoint control which may involve signaling of damage to **p53**.

L34 ANSWER 3 OF 10 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2003:401262 BIOSIS
DOCUMENT NUMBER: PREV200300401262
TITLE: Normal tissue radiosensitivity of cancer patients is not commonly associated with a constitutional dysfunction of the **p53**- or **mre11**/rad50/nibrin-mediated pathways in DNA double strand break repair.
AUTHOR(S): Bigalke, M. [Reprint Author]; Bendix, R. [Reprint Author]; Stumm, M.; Dahm-Daphi, J.; Rave-Fraenk, M.; Schindler, D.; Bremer, M. [Reprint Author]; Rades, D. [Reprint Author]; Karstens, J. H. [Reprint Author]; Doerk, T. [Reprint Author]
CORPORATE SOURCE: Medizinische Hochschule, Hannover, Germany
doerk.thilo@mh-hannover.de
SOURCE: European Journal of Human Genetics, (2001) Vol. 9, No. Supplement 1, pp. P0019. print.
Meeting Info.: 10th International Congress of Human Genetics. Vienna, Austria. May 15-19, 2001. International Federation of Human Genetics Societies.
ISSN: 1018-4813.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 3 Sep 2003
Last Updated on STN: 3 Sep 2003

L34 ANSWER 4 OF 10 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2000:369661 BIOSIS
DOCUMENT NUMBER: PREV200000369661
TITLE: Polymerase eta deficiency in the xeroderma pigmentosum variant uncovers an overlap between the S phase checkpoint and double-strand break repair.
AUTHOR(S): Limoli, Charles L.; Giedzinski, Erich; Morgan, William F.; Cleaver, James E. [Reprint author]
CORPORATE SOURCE: Department of Dermatology, Cancer Center, University of California, San Francisco, CA, 94143-0808, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (July 5, 2000) Vol. 97, No. 14, pp. 7939-7946. print.
CODEN: PNASA6. ISSN: 0027-8424.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 30 Aug 2000
Last Updated on STN: 8 Jan 2002
AB The xeroderma pigmentosum variant (XPV) is a genetic disease involving high levels of solar-induced cancer that has normal excision repair but shows defective DNA replication after UV irradiation because of mutations in the damage-specific polymerase hRAD30. We previously found that the induction of sister chromatid exchanges by UV irradiation was greatly

L17 ANSWER 37 OF 38 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 1981:139968 BIOSIS
DOCUMENT NUMBER: PREV198171009960; BA71:9960
TITLE: SURVIVAL OF HUMAN LYMPHO BLASTOID CELLS AFTER **DNA DAMAGE** MEASURED BY GROWTH IN MICRO TITER WELLS.
AUTHOR(S): KRAEMER K H [Reprint author]; WATERS H L; BUCHANAN J K
CORPORATE SOURCE: LAB MOL CARCINOGENESIS, NATL CANCER INST, BETHESDA, MD 20205, USA
SOURCE: Mutation Research, (1980) Vol. 72, No. 2, pp. 285-294. CODEN: MUREAV. ISSN: 0027-5107.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: ENGLISH

AB Survival of cells in suspension culture after treatment with damaging agents is usually measured by extrapolation from growth curves or by growth of colonies in soft agar. A survial assay was developed which measures the ability of small numbers of cells to initiate microscopic cultures in wells of microtiter plates without agar or feeder layers. Suitable human lymphoblastoid lines were obtained by selection of rapidly growing cultures from microtiter wells in which < 200 cells were inoculated in 0.2 ml RPMI 1640 medium and incubated at 37° with 5% CO2 at 95% relative humidity. Survival after damage was measured by inoculating groups of 24 microtiter wells with appropriate serial dilutions of cells. The wells were examined microscopically at intervals and scored for evidence of **cell proliferation**.
Survival was calculated with the Poisson formula on the basis of the fraction of wells in which cells were not proliferating. Survival did not change appreciably after 2-3 wk incubation. Survival measured by the microtiter-well assay was similar to survival measured by extrapolation from growth curves after damaging the cells with **bleomycin** or with 8-methoxypsoralen plus long-wavelength UV radiation. The microtiter-well assay affords a simple, accurate measure of **cell** survival in human lymphoblastoid cells with suitable growth ability.

L17 ANSWER 34 OF 38 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 1996:63149 BIOSIS
DOCUMENT NUMBER: PREV199698635284
TITLE: P53 Functional loss in a colon cancer **cell** line with two missense mutations (218leu and 248trp) on separate alleles.
AUTHOR(S): Rand, A.; Glenn, K. S.; Alvares, C. P.; White, M. B.; Thibodeau, S. M.; Karnes, W. E., Jr. [Reprint author]
CORPORATE SOURCE: Dep. Med., Div. Gastroenterol., GI Res. Unit, Mayo Clin., Rochester, MN 55905, USA
SOURCE: Cancer Letters, (1996) Vol. 98, No. 2, pp. 183-191. CODEN: CALEDQ. ISSN: 0304-3835.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 9 Feb 1996
Last Updated on STN: 9 Feb 1996

AB We have sequenced p53 in three colon cancer **cell** lines capable of autonomous **proliferation**. SNU-C1 and SNU-C4 cells, whose autonomous growth is dependent upon autocrine stimulation of epidermal growth factor receptor (EGFR), had wild-type p53 sequence of exons 4-9. In contrast, an EGFR ligand-independent **cell** line, SNU-C5, had heterozygous missense mutations affecting codons 218 (valine to leucine) and 248 (arginine to tryptophan) of p53. Bacterial cloning of p53 from SNU-C5 cells showed that the 248trp and 218leu mutants were both expressed and on separate alleles. 248trp is a common 'hot spot' mutant of p53 with variable dominant negative activity depending on the cellular context. Valine 218, in contrast, is rarely affected by mutation in cancers and is located in a region of the hydrophobic core domain away from 'hot spot' DNA contact sights. However, valine 218 is completely conserved across species, prompting us to investigate the function of 218leu in SNU-C5 cells. SNU-C5 cells exhibited complete loss of normal p53 function as evidenced by over-expression of p53 protein and by failure to show induction of p53, waf-1, mdm-2 or G1/S arrest in response to the DNA damaging agent, **bleomycin**. In a yeast p53 functional assay (FASAY), 50% of the clones were unable to transactivate a p53-specific promoter required for yeast colony expansion at 25, 30 or 37 degree C. Sequencing of the p53 insert from several randomly selected wild-type and mutant yeast clones revealed that 218leu-bearing clones retained their ability to transactivate the p53-specific promoter. As expected, the 248trp-bearing clones lost this function. These data indicate that although 218leu retains normal transactivation activity on a p53 promoter in yeast at physiological temperatures, it is not capable of normal p53 function in the presence of a 248trp allele in SNU-C5 cells. It remains unclear whether the strong dominant negative activity of 248trp in SNU-C5 cells is related to the cellular context or to an unresolved abnormality of 218leu function.

L17 ANSWER 21 OF 38 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 1998091910 EMBASE

TITLE: Agents that cause DNA double strand breaks lead to p16(INK4a) enrichment and the premature senescence of normal fibroblasts.

AUTHOR: Robles S.J.; Adami G.R.

CORPORATE SOURCE: G.R. Adami, Ctr. Molecular Biology Oral Diseases, College of Dentistry, University of Illinois at Chicago, Chicago, IL 60612, United States

SOURCE: Oncogene, (5 Mar 1998) Vol. 16, No. 9, pp. 1113-1123.
Refs: 84
ISSN: 0950-9232 CODEN: ONCNES

COUNTRY: United Kingdom

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 016 Cancer
021 Developmental Biology and Teratology
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 19980409
Last Updated on STN: 19980409

AB The occurrence of DNA double strand breaks induces **cell** cycle arrest in mortal and immortal human cells. In normal, mortal fibroblasts this block to **proliferation** is permanent. It depends on the growth regulator p53 and a protein p53 induces, the cyclin dependent kinase inhibitor, p21. We show here that following **DNA damage** in mortal fibroblasts, the induction of p21 and p53 is to a large degree shortlived. By 8 days after a brief exposure to DNA strand breaking agents, **bleomycin** or actinomycin D, p53 protein is at baseline levels, while the p53 transactivation level is only slightly above its baseline. By this time the concentration of p21 protein, which goes up as high as 100-fold shortly after treatment, is down to just 2-4-fold over baseline levels. Following the drop in p21 concentration a large increase in the expression level of the tumor suppressor gene p16(INK4a) is observed. This scenario, where a transient increase in p21 is followed by a delayed induction of p16(INK4a), also happens with the permanent arrest that occurs with cellular senescence. In fact, these cells treated with agents that cause DNA double strand breaks share a number of additional markers with senescent cells. Our findings indicate that these cells are very similar to senescent cells and that they have additional factor(s) beside p21 and p53 that maintain **cell** cycle arrest.

2002/0124279 -Mahajan

[0005] In summary, MRE11 is an important gene involved in meiotic and mitotic recombination, as well as homologous and non-homologous recombination. Thus, this single protein participates in multiple pathways that are often competing with each other such as double-strand break (DSB) formation in meiosis and DSB repair (via non-homologous end joining pathway) in mitosis. A very recent study by Furuse M, et al. employed two specific mutants of yeast Mre11 to elucidate this phenomenon (Furuse M, et al. EMBO J. 17:6412-6425; 1998). A point mutation in Mre11 (Asp16Ala) completely abolished the nuclease activity, without any change in DNA binding activity. This mutation also conferred MMS sensitivity to mitotic cells and caused them to accumulate unprocessed DSBs during meiosis. However, another mutant carrying a deletion of 49 C-terminal amino acids had almost wild-type levels of nuclease activity but reduced DNA binding activity. The mitotic phenotypes of this mutant were essentially unchanged, but the meiotic DSB formation was reduced dramatically. These results indicate the presence of two distinct functional domains on the Mre11 protein, an N-terminal region specifically involved in mitotic functions and a C-terminal 49 amino acid domain involved in the meiotic DSB formation. Thus, interactions of different domains with other proteins (such as Rad50 and Xrs2/P95) may be an underlying mechanism for the distinct roles of Mre11 in meiosis and mitosis (Usui T et al., Cell 95:705-716, 1998). Whatever mechanisms may be involved, it is clear that either null or the N-terminal nuclease domain mutants of Mre11 are deficient in non-homologous end-joining.

identified using the C-terminal region of human Rad50 as the bait in a yeast two-hybrid **screen**. Human RINT-1 shares sequence homology with a novel protein identified in Drosophila melanogaster, including a coiled-coil domain within its N-terminal 150 amino acids, a conserved central domain of about 350 amino acids, and a C-terminal region of 90 amino acids exhibiting 35-38% identity. The conserved central and C-terminal regions of RINT-1 are required for its interaction with Rad50. While Rad50 and RINT-1 are both expressed throughout the cell cycle, RINT-1 specifically binds to Rad50 only during late S and G(2)/M phases, suggesting that RINT-1 may be involved in cell cycle regulation. Consistent with this possibility, MCF-7 cells expressing an N-terminally truncated RINT-1 protein displayed a defective radiation-induced G(2)/M checkpoint. These results suggest that RINT-1 may play a role in the regulation of cell cycle control after DNA damage.

L18 ANSWER 3 OF 9 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2001465194 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11511367
TITLE: **Mre11 protein** complex prevents double-strand break accumulation during chromosomal DNA replication.
AUTHOR: Costanzo V; Robertson K; Bibikova M; Kim E; Grieco D; Gottesman M; Carroll D; Gautier J
CORPORATE SOURCE: Department of Genetics and Development, Columbia University, New York, NY 10032, USA.
CONTRACT NUMBER: RO1 GM56781 (NIGMS)
SOURCE: Molecular cell, (2001 Jul) 8 (1) 137-47.
Journal code: 9802571. ISSN: 1097-2765.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200109
ENTRY DATE: Entered STN: 20010821
Last Updated on STN: 20010917
Entered Medline: 20010913
AB **Mre11** complex promotes repair of DNA double-strand breaks (DSBs). Xenopus **Mre11** (X-**Mre11**) has been cloned, and its role in DNA replication and DNA damage checkpoint studied in cell-free extracts. DSBs stimulate the phosphorylation and 3'-5' exonuclease activity of X-**Mre11** complex. This induced phosphorylation is ATM independent. Phosphorylated X-**Mre11** is found associated with replicating nuclei. X-**Mre11** complex is required to yield normal DNA replication products. Genomic DNA replicated in extracts immunodepleted of X-**Mre11** complex accumulates DSBs as demonstrated by TUNEL **assay** and reactivity to phosphorylated histone H2AX antibodies. In contrast, the ATM-dependent DNA damage checkpoint that blocks DNA replication initiation is X-**Mre11** independent. These results strongly suggest that the function of X-**Mre11** complex is to repair DSBs that arise during normal DNA replication, thus unraveling a critical link between recombination-dependent repair and DNA replication.

L18 ANSWER 4 OF 9 MEDLINE on STN
ACCESSION NUMBER: 2001090377 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11095674
TITLE: Alteration of gene conversion tract length and associated crossing over during plasmid gap repair in nuclease-deficient strains of Saccharomyces cerevisiae.
AUTHOR: Symington L S; Kang L E; Moreau S
CORPORATE SOURCE: Department of Microbiology and Institute of Cancer Research, Columbia University College of Physicians and Surgeons, 701 West 168th Street, New York, NY 10032, USA.. lss5@columbia.edu
CONTRACT NUMBER: GM54099 (NIGMS)
SOURCE: Nucleic acids research, (2000 Dec 1) 28 (23) 4649-56.
Journal code: 0411011. ISSN: 1362-4962.
PUB. COUNTRY: ENGLAND: United Kingdom

L18 ANSWER 1 OF 9 MEDLINE on STN
ACCESSION NUMBER: 2001490882 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11533244
TITLE: Intrachromatid excision of telomeric DNA as a mechanism for telomere size control in Saccharomyces cerevisiae.
AUTHOR: Bucholc M; Park Y; Lustig A J
CORPORATE SOURCE: Department of Biochemistry, Tulane University Health Sciences Center, New Orleans, Louisiana 70112, USA.
CONTRACT NUMBER: GM56526 (NIGMS)
SOURCE: Molecular and cellular biology, (2001 Oct) 21 (19) 6559-73. Journal code: 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200109
ENTRY DATE: Entered STN: 20010905
Last Updated on STN: 20030218
Entered Medline: 20010927

AB We have previously identified a process in the yeast Saccharomyces cerevisiae that results in the contraction of elongated telomeres to wild-type length within a few generations. We have termed this process telomeric rapid deletion (TRD). In this study, we use a combination of physical and genetic assays to investigate the mechanism of TRD. First, to distinguish among several recombinational and nucleolytic pathways, we developed a novel physical **assay** in which HaeIII restriction sites are positioned within the telomeric tract. Specific telomeres were subsequently tested for HaeIII site movement between telomeres and for HaeIII site retention during TRD. Second, genetic analyses have demonstrated that mutations in RAD50 and **MRE11** inhibit TRD. TRD, however, is independent of the Rap1p C-terminal domain, a central regulator of telomere size control. Our results provide evidence that TRD is an intrachromatid deletion process in which sequences near the extreme terminus invade end-distal sequences and excise the intervening sequences. We propose that the Mre11p-Rad50p-Xrs2p complex prepares the invading telomeric overhang for strand invasion, possibly through end processing or through alterations in chromatin structure.

L18 ANSWER 2 OF 9 EMBASE
ACCESSION NUMBER: 2003454098 EMBASE
TITLE: RINT-1, a Novel Rad50-interacting Protein, Participates in Radiation-induced G(2)/M Checkpoint Control.
AUTHOR: Xiao J.; Liu C.-C.; Chen P.-L.; Lee W.-H.
CORPORATE SOURCE: W.-H. Lee, Department of Molecular Medicine, Institute of Biotechnology, Univ. of Texas Hlth. Science Center, San Antonio, TX 78245-3207, United States. Leew@uthscsa.edu
SOURCE: Journal of Biological Chemistry, (2 Mar 2001) Vol. 276, No. 9, pp. 6105-6111.
Refs: 39
ISSN: 0021-9258 CODEN: JBCHA3
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20031204
Last Updated on STN: 20031204

AB Rad50, an structural maintenance of chromosomes (SMC) protein family member, participates in a variety of cellular processes, including DNA double-strand break repair, cell cycle checkpoint activation, telomere maintenance, and meiosis. Disruption of Rad50 in mice leads to lethality during early embryogenesis, indicating its essential function in normal proliferating cells. In addition to its ability to form a complex with the DNA double-strand break repair proteins **Mre11** and NBS1, Rad50 may interact with other cellular proteins to execute its full range of biological activities. A novel 87-kDa protein named RINT-1 was

L39 ANSWER 1 OF 3 MEDLINE on STN
ACCESSION NUMBER: 2001222041 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11311215
TITLE: N-Nitrosomorpholine induced alterations of unscheduled DNA synthesis, mitochondrial DNA synthesis and cell proliferation in different cell types of liver, kidney, and urogenital organs in the rat.
AUTHOR: Korr H; Botzem B; Schmitz C; Enzmann H
CORPORATE SOURCE: Department of Anatomy and Cell Biology, RWTH University of Aachen, Pauwelsstrasse/Wendlingweg 2, D-52057, Aachen, Germany.. hkorr@post.klinikum.rwth-aachen.de
SOURCE: Chemico-biological interactions, (2001 Apr 16) 134 (2) 217-33.
Journal code: 0227276. ISSN: 0009-2797.
PUB. COUNTRY: Ireland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200105
ENTRY DATE: Entered STN: 20010604
Last Updated on STN: 20010604
Entered Medline: 20010531

AB In order to **measure** rates of unscheduled DNA **synthesis** (UDS), mitochondrial DNA **synthesis**, and **cell proliferation**, i.e. factors relevant in the early phase of carcinogenesis, young rats received by gavage 200 mg/kg N-nitrosomorpholine (NNM) or vehicle (distilled water), and were injected with 3H-thymidine 24 h later. Autoradiographs from liver, kidney, urethra, prostate, seminal vesicle, and ductus deferens were prepared from deparaffinized sections, using a 250-day exposure time. In the liver, UDS was at least doubled in 2n and 4n hepatocytes. Approximately 3% of these hepatocytes exhibited a fourfold increase in UDS. Such strongly labeled cells were only observed in the liver following NNM exposure. With the exception of renal epithelial cells of the proximal tubule, UDS in epithelial cells of bladder, urethra, ductus deferens, seminal vesicle and prostate was decreased in NNM-exposed rats. Mitochondrial DNA synthesis and **cell proliferation** were significantly increased only in hepatocytes, and were decreased in all other monitored organs in NNM-exposed rats. The strongly increased UDS and more moderately increased mitochondrial DNA synthesis in a subgroup of hepatocytes suggest that possibly some unrepaired damage persists in the DNA of these cells. The latter cells may be the precursors of so-called foci of hepatocellular alteration, which appear later during the process of carcinogenesis. The increased UDS but decreased rate of proliferation in the renal proximal tubule cells might be related to renal carcinogenesis which is observed in NNM-exposed rats after a long latency period.

L39 ANSWER 2 OF 3 MEDLINE on STN
ACCESSION NUMBER: 1999194233 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10096569
TITLE: Monoclonal antibody to HER-2/neureceptor modulates repair of radiation-induced DNA damage and enhances radiosensitivity of human breast cancer cells overexpressing this oncogene.
AUTHOR: Pietras R J; Poen J C; Gallardo D; Wongvipat P N; Lee H J; Slamon D J
CORPORATE SOURCE: Department of Medicine, UCLA School of Medicine, Los Angeles, California 90095, USA.
CONTRACT NUMBER: P01-CA32737 (NCI)
R01-CA36827 (NCI)
R29-CA60835 (NCI)
SOURCE: Cancer research, (1999 Mar 15) 59 (6) 1347-55.
Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals

ENTRY MONTH: 199904
ENTRY DATE: Entered STN: 19990426
Last Updated on STN: 20000303
Entered Medline: 19990413

AB The management of human breast cancer frequently includes radiation therapy as an important intervention, and improvement in the clinical efficacy of radiation is desirable. Overexpression of the HER-2 growth factor receptor occurs in 25-30% of human breast cancers and correlates with poor clinical outcome, including earlier local relapse following conservative surgery accompanied by radiation therapy. In breast cancer cells with overexpression of HER-2 receptor, recombinant humanized monoclonal antibodies (rhuMAbs) to HER-2 receptors (rhuMAb HER-2) decrease **cell proliferation** in vitro and reduce tumor formation in nude mice. Therapy with rhuMAb HER-2 enhances tumor sensitivity to radiation at doses of 1-5 Gy, exceeding remission rates obtained with radiation alone. This benefit is specific to cells with HER-2 overexpression and does not occur in cells without overexpression. Treatment of cells with radiation (2-4 Gy) alone provokes a marked increase in unscheduled DNA **synthesis**, a **measure** of **DNA repair**, but HER-2-overexpressing cells treated with a combination of rhuMAb HER-2 and radiation demonstrate a decrease of unscheduled DNA **synthesis** to 25-44% of controls. Using an alternate test of **DNA repair**, i.e., radiation-damaged or undamaged reporter DNA, we introduced a cytomegalovirus-driven beta3-galactosidase into HER-2-overexpressing breast cancer cells that had been treated with rhuMAb HER-2 or control. At 24 h posttransfection, the extent of repair assayed by measuring reporter DNA expression was high after exposure to radiation alone but significantly lower in cells treated with combined radiation and rhuMAb HER-2 therapy. To further characterize effects of rhuMAb HER-2 and the combination of antibody and radiation on cell growth, analyses of cell cycle phase distribution were performed. Antibody reduces the fraction of HER-2-overexpressing breast cancer cells in S phase at 24 and 48 h. Radiation treatment is also known to promote cell cycle arrest, predominantly at G1, with low S-phase fraction at 24 and 48 h. In the presence of rhuMAb HER-2, radiation elicits a similar reduction in S phase at 24 h, but a significant reversal of this arrest appears to begin 48 h postradiation exposure. The level of S-phase fraction at 48 h is significantly greater than that found at 24 h with the combined antibody-radiation therapy, suggesting that early escape from cell cycle arrest in the presence of antireceptor antibody may not allow sufficient time for completion of **DNA repair** in HER-2-overexpressing cells. Because it is well known that failure of adequate p21WAF1 induction after DNA damage is associated with failure of cell cycle arrest, we also assessed the activity of this critical mediator of the cellular response to DNA damage. The results show induction of p21WAF1 transcripts and protein product at 6, 12, and 24 h after radiation treatment; however, increased levels of p21WAF1 transcript and protein are not sustained in HER-2-overexpressing cells exposed to radiation in the presence of rhuMAb HER-2. Although transcript and protein levels increase at 6-12 h, they are both diminished by 24 h. Levels of p21WAF1 transcript and protein at 24 h are significantly lower than in cells treated by radiation without antibody. A reduction in the basal level of p21WAF1 transcript also occurred after 12-24 h exposure to antibody alone. The effect of HER-2 antibody may be related to tyrosine phosphorylation of p21WAF1 protein. Tyrosine phosphorylation of p21WAF1 is increased after treatment with radiation alone, but phosphorylation is blocked by combined treatment with antireceptor antibody and radiation. This dysregulation of p21WAF1 in HER-2-overexpressing breast cells after treatment with rhuMAb HER-2 and radiation appears to be independent of p53 expression levels but does correlate with reduced levels of mdm2 protein. (ABSTRACT TRUNCATED)

L39 ANSWER 3 OF 3 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 1992:286574 BIOSIS
DOCUMENT NUMBER: PREV199294011224; BA94:11224
TITLE: LUNG INJURY DUE TO HYPEROXIA IN YOUNG AND ADULT RATS.
AUTHOR(S): JINNO S [Reprint author]
CORPORATE SOURCE: DEP MED I, TOKYO WOMEN'S MED COLL, PULMONARY DIV, TOKYO METROPOLITAN GERIATRIC HOSP, JPN

SOURCE: Journal of Tokyo Women's Medical College, (1992) Vol. 62, No. 1, pp. 10-16.
CODEN: TJIZAF. ISSN: 0040-9022.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: JAPANESE
ENTRY DATE: Entered STN: 10 Jun 1992
Last Updated on STN: 10 Jun 1992

AB It has been known that immature rats survive longer than mature rats under hyperoxia. Recent studies indicate that DNA biosynthesis and **cell proliferation** might be important in the development of oxygen tolerance. To clarify the hypothesis that DNA replication and repair might differ between mature and immature rat lungs, we studied DNA polymerase (DNA-pol) activity and its molecular forms in lung cells after oxygen exposure. DNA-pol activity in immature rat lungs increased during hyperoxic exposure, whereas DNA-pol activity in mature rat lungs decreased. DNA-pol β, which is thought to be related to nuclear **DNA repair**, and DNA-pol γ, believed to be related to mitochondrial DNA replication, appeared only in immature rat lungs, but not in mature rat lungs. As a **measure** of DNA **synthesis**, the number of lung cells was found to increase only in immature rat lungs. We conclude that nuclear **DNA repair** and mitochondrial DNA replication are well preserved in immature rat lungs and that these facts may account for the oxygen tolerance.

=>

the SIR gene products ensues through an error-prone DNA repair pathway that results in terminal deletions. To identify novel components of the Ku-associated DSB repair pathway, we have tested several other candidate genes for their involvement in DNA DSB repair, telomeric maintenance and TPE. We show that TEL1, a gene required for telomeric length maintenance, is not required for either DNA DSB repair or TPE. However, RAD50, **MRE11** and XRS2 function both in Ku-dependent DNA DSB repair and in telomeric length maintenance, although they have no major effects on TPE. These data provide important insights into DNA DSB repair and the linkage of this process to telomere length homeostasis and transcriptional silencing.

L18 ANSWER 8 OF 9 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 97447802 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9303542
TITLE: mre11S--a yeast mutation that blocks double-strand-break processing and permits nonhomologous synapsis in meiosis.
AUTHOR: Nairz K; Klein F
CORPORATE SOURCE: Institut fur Botanik, Abteilung fur Zytologie und Genetik, Vienna, Austria.
SOURCE: Genes & development, (1997 Sep 1) 11 (17) 2272-90.
Journal code: 8711660. ISSN: 0890-9369.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-S57592; GENBANK-U60829
ENTRY MONTH: 199710
ENTRY DATE: Entered STN: 19971105
Last Updated on STN: 20030218
Entered Medline: 19971020

AB During meiotic prophase the repair of self-inflicted DNA double-strand break (DSB) damage leads to meiotic recombination in yeast. We employed a genetic **screen** to specifically characterize cellular functions that become essential after this DSB formation. As a result a new allele of **MRE11**, termed mre11S (for Separation of functions) was isolated that allows initiation but not processing and repair of meiotic DSBs similar to the well-characterized rad50S allele. In contrast, the **mre11**-1 allele blocks initiation of meiotic DSBs as reported previously by others. The mre11S allele, which is mutated in the 5' part of the gene, can partially complement **mre11** alleles disrupted close to the 3' end that cannot initiate DSBs when homozygous. This suggests homodimerization of the **Mre11 protein** and the presence of separate domains for DSB initiation and 5' resection. The fact that two genes, RAD50 and **MRE11**, required for DSB processing are also essential for DSB initiation dictates a model in which a bifunctional initiation/repair complex is required to initiate meiotic recombination. A subset of mre11S nuclei was shown to perform extensive but partially nonhomologous synapsis. We propose that the unprocessed DSBs present in mre11S allow for synapsis, but that homologous synapsis is only ensured at a later stage of recombination.

L18 ANSWER 9 OF 9 MEDLINE on STN
ACCESSION NUMBER: 96079094 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8530104
TITLE: Isolation and characterization of the human MRE11 homologue.
AUTHOR: Petrini J H; Walsh M E; DiMare C; Chen X N; Korenberg J R; Weaver D T
CORPORATE SOURCE: Division of Tumor Immunology, Dana-Farber Cancer Institute, Boston, Massachusetts, USA.
CONTRACT NUMBER: CA52694 (NCI)
R29HG00037 (NHGRI)
SOURCE: Genomics, (1995 Sep 1) 29 (1) 80-6.
Journal code: 8800135. ISSN: 0888-7543.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English

FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-U37359
ENTRY MONTH: 199602
ENTRY DATE: Entered STN: 19960220
Last Updated on STN: 20030218
Entered Medline: 19960201

AB Mutation of the Saccharomyces cerevisiae RAD52 epistasis group gene, **MRE11**, blocks meiotic recombination, confers profound sensitivity to double-strand break damage, and has a hyperrecombinational phenotype in mitotic cells. We isolated a highly conserved human **MRE11** homologue using a two-hybrid **screen** for DNA ligase I-interacting proteins. Human **MRE11** shares approximately 50% identity with its yeast counterpart over the N-terminal half of the protein. **MRE11** is expressed at the highest levels in proliferating tissues, but is also observed in other tissues. The **MRE11** locus maps to human chromosome 11q21 in a region frequently associated with cancer-related chromosomal abnormalities. A **MRE11**-related locus was found on chromosome 7q11.2-q11.3.

=>

L7 ANSWER 1 OF 1 MEDLINE on STN DUPLICATE 1

ACCESSION NUMBER: 2000094337 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10630641
TITLE: DNA damage-induced cell cycle checkpoints and DNA strand break repair in development and tumorigenesis.
AUTHOR: Dasika G K; Lin S C; Zhao S; Sung P; Tomkinson A; Lee E Y
CORPORATE SOURCE: Department of Molecular Medicine, Institute of Biotechnology, University of Texas Health Science Center at San Antonio, 78245, USA.
CONTRACT NUMBER: 1R01NS378381 (NINDS)
SOURCE: Oncogene, (1999 Dec 20) 18 (55) 7883-99. Ref: 202
Journal code: 8711562. ISSN: 0950-9232.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200001
ENTRY DATE: Entered STN: 20000131
Last Updated on STN: 20000131
Entered Medline: 20000120

AB Several newly identified tumor suppressor genes including ATM, NBS1, BRCA1 and BRCA2 are involved in DNA double-strand break repair (**DSBR**) and DNA damage-induced checkpoint activation. Many of the gene products involved in checkpoint control and **DSBR** have been studied in great detail in yeast. In addition to evolutionarily conserved proteins such as Chk1 and Chk2, studies in mammalian cells have identified novel proteins such as p53 in executing checkpoint control. **DSBR** proteins including **Mre11**, Rad50, Rad51, Rad54, and Ku are present in yeast and in mammals. Many of the tumor suppressor gene products interact with these repair proteins as well as checkpoint regulators, thus providing a biochemical explanation for the pleiotropic phenotypes of mutant cells. This review focuses on the proteins mediating G1/S, S, and G2/M checkpoint control in mammalian cells. In addition, mammalian **DSBR** proteins and their activities are discussed. An intricate network among DNA damage signal transducers, cell cycle regulators and the **DSBR** pathways is illustrated. Mouse knockout models for genes involved in these processes have provided valuable insights into their function, establishing genomic instability as a major contributing factor in tumorigenesis.

=>

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200101
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20030218
Entered Medline: 20010125

AB A plasmid gap repair **assay** was used to assess the role of three known nucleases, Exo1, **Mre11** and Rad1, in the processing of DNA ends and resolution of recombination intermediates during double-strand gap repair. In this **assay**, alterations in end processing or branch migration are reflected by the frequency of co-conversion of a chromosomal marker 200 bp from the gap. Gap repair associated with crossing over results in integration at the homologous chromosomal locus, whereas the plasmid remains episomal for non-crossover repair events. In **mre11** strains, the frequency of gap repair was reduced 3- to 10-fold and conversion tracts were shorter than in the wild-type strain, consistent with a role for this nuclease in processing double-strand breaks. However, conversion tracts were longer in a strain containing the nuclease deficient allele, **mre11**-H125N, suggesting increased end processing by redundant nucleases. The frequency of gap repair was reduced 2-fold in rad1 mutants and crossing over was reduced, consistent with a role for Rad1 in cleaving recombination intermediates. The frequency of gap repair was increased in exo1 mutants with a significant increase in crossing over. In exo1 **mre11** double mutants gap repair was reduced to below the **mre11** single mutant level.

L18 ANSWER 5 OF 9 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 1999:299826 BIOSIS
DOCUMENT NUMBER: PREV199900299826
TITLE: Formation of the yeast Mre11-Rad50-Xrs2 complex is correlated with DNA repair and telomere maintenance.
AUTHOR(S): Chamankhah, Mahmood; Xiao, Wei [Reprint author]
CORPORATE SOURCE: Department of Microbiology and Immunology, University of Saskatchewan, 107 Wiggins Road, Saskatoon, SK, S7N 5E5, Canada
SOURCE: Nucleic Acids Research, (May 15, 1999) Vol. 27, No. 10, pp. 2072-2079. print.
CODEN: NARHAD. ISSN: 0305-1048.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 12 Aug 1999
Last Updated on STN: 12 Aug 1999

AB The yeast Mre11 is a multi-functional protein and is known to form a protein complex with Rad50 and Xrs2. In order to elucidate the relationship between Mre11 complex formation and its mitotic functions, and to determine domain(s) required for **Mre11 protein** interactions, we performed yeast two-hybrid and functional analyses with respect to Mre11 DNA repair and telomere maintenance. Evidence presented in this study indicates that the N-terminal region of Mre11 constitutes the core homo-dimerization and heterodimerization domain and is sufficient for Mre11 DNA repair and maintaining the wild-type telomere length. In contrast, a stretch of 134 amino acids from the extreme C-terminus, although essential for achieving a full level of self-association, is not required for the aforementioned Mre11 mitotic functions. Interestingly, deletion of these same 134 amino acids enhanced the interaction of Mre11 with Rad50 and Xrs2, which is consistent with the notion that this region is specific for meiotic functions. While Mre11 self-association alone is insufficient to provide the above mitotic activities, our results are consistent with a strong correlation between Mre11-Rad50-Xrs2 complex formation, mitotic DNA repair and telomere maintenance. This correlation was further strengthened by analyzing two mre11 phosphoesterase motif mutants (mre11-2 and rad58S), which are defective in DNA repair, telomere maintenance and protein interactions, and a rad50S mutant, which is normal in both complex formation and mitotic functions. Together, these results support and extend a current model regarding Mre11 structure and functions in mitosis and meiosis.

L18 ANSWER 6 OF 9 MEDLINE on STN
ACCESSION NUMBER: 1999400558 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10471504
TITLE: Gross chromosomal rearrangements in Saccharomyces cerevisiae replication and recombination defective mutants.
AUTHOR: Chen C; Kolodner R D
CORPORATE SOURCE: Ludwig Institute for Cancer Research, Cancer Center and Department of Medicine, University of California-San Diego School of Medicine, La Jolla, California 92093, USA.
CONTRACT NUMBER: GM26017 (NIGMS)
GM50006 (NIGMS)
SOURCE: Nature genetics, (1999 Sep) 23 (1) 81-5.
Journal code: 9216904. ISSN: 1061-4036.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199909
ENTRY DATE: Entered STN: 19991005
Last Updated on STN: 20030218
Entered Medline: 19990923

AB Cancer progression is often associated with the accumulation of gross chromosomal rearrangements (GCRs), such as translocations, deletion of a chromosome arm, interstitial deletions or inversions. In many instances, GCRs inactivate tumour-suppressor genes or generate novel fusion proteins that initiate carcinogenesis. The mechanism underlying GCR formation appears to involve interactions between DNA sequences of little or no homology. We previously demonstrated that mutations in the gene encoding the largest subunit of the Saccharomyces cerevisiae single-stranded DNA binding protein (RFA1) increase microhomology-mediated GCR formation. To further our understanding of GCR formation, we have developed a novel mutator **assay** in S. cerevisiae that allows specific detection of such events. In this **assay**, the rate of GCR formation was increased 600-5, 000-fold by mutations in RFA1, RAD27, **MRE11**, XRS2 and RAD50, but was minimally affected by mutations in RAD51, RAD54, RAD57, YKU70, YKU80, LIG4 and POL30. Genetic analysis of these mutants suggested that at least three distinct pathways can suppress GCRs: two that suppress microhomology-mediated GCRs (RFA1 and RAD27) and one that suppresses non-homology-mediated GCRs (RAD50/**MRE11**/XRS2).

L18 ANSWER 7 OF 9 MEDLINE on STN
ACCESSION NUMBER: 1998169398 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9501103
TITLE: Components of the Ku-dependent non-homologous end-joining pathway are involved in telomeric length maintenance and telomeric silencing.
AUTHOR: Boulton S J; Jackson S P
CORPORATE SOURCE: Wellcome/CRC Institute, Tennis Court Road, Cambridge CB2 1QR, UK.
SOURCE: EMBO journal, (1998 Mar 16) 17 (6) 1819-28.
Journal code: 8208664. ISSN: 0261-4189.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199804
ENTRY DATE: Entered STN: 19980507
Last Updated on STN: 20030218
Entered Medline: 19980424

AB In the budding yeast, Saccharomyces cerevisiae, genes in close proximity to telomeres are subject to transcriptional silencing through the process of telomere position effect (TPE). Here, we show that the protein Ku, previously implicated in DNA double-strand break (DSB) repair and in telomeric length maintenance, is also essential for telomeric silencing. Furthermore, using an in vivo plasmid rejoining **assay**, we demonstrate that SIR2, SIR3 and SIR4, three genes shown previously to function in TPE, are essential for Ku-dependent DSB repair. As is the case for Ku-deficient strains, residual repair operating in the absence of

L29 ANSWER 1 OF 1 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 1999276558 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10346816
TITLE: Nbs1 potentiates ATP-driven DNA unwinding and endonuclease cleavage by the Mre11/Rad50 complex.
AUTHOR: Paull T T; Gellert M
CORPORATE SOURCE: Laboratory of Molecular Biology, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland 20892-0540, USA.
SOURCE: Genes & development, (1999 May 15) 13 (10) 1276-88.
Journal code: 8711660. ISSN: 0890-9369.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199906
ENTRY DATE: Entered STN: 19990712
Last Updated on STN: 20030218
Entered Medline: 19990624

AB The Nijmegen breakage syndrome gene product (Nbs1) was shown recently to associate in vivo with the Mre11 and Rad50 proteins, which play pivotal roles in eukaryotic DNA double-strand break repair, meiotic recombination, and telomere maintenance. We show in this work that the triple complex of **recombinant** Nbs1, **Mre11**, and Rad50 proteins binds cooperatively to DNA and forms a distinct protein-DNA species. The Mre11/Rad50/Nbs1 complex displays several enzymatic activities that are not seen without Nbs1, including partial unwinding of a DNA duplex and efficient cleavage of fully paired hairpins. Unwinding and hairpin cleavage are both increased by the presence of ATP. On nonhairpin DNA ends, ATP controls a switch in endonuclease specificity that allows Mre11/Rad50/Nbs1 to cleave a 3'-protruding strand at a double-/single-strand transition. Mutational analysis demonstrates that Rad50 is responsible for ATP binding by the complex, but the ATP-dependent activities are expressed only with Nbs1 present.

=>

L10 ANSWER 3 OF 3 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2001297838 EMBASE

TITLE: **Mre11** protein complex prevents double-strand break accumulation during chromosomal DNA replication.

AUTHOR: Costanzo V.; Robertson K.; Bibikova M.; Kim E.; Grieco D.; Gottesman M.; Carroll D.; Gautier J.

CORPORATE SOURCE: J. Gautier, Department of Genetics, Columbia University, New York, NY 10032, United States. jg130@columbia.edu

SOURCE: Molecular Cell, (2001) Vol. 8, No. 1, pp. 137-147.
Refs: 52
ISSN: 1097-2765 CODEN: MOCEFL

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 022 Human Genetics
029 Clinical Biochemistry

LANGUAGE: English

SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 20010906
Last Updated on STN: 20010906

AB **Mre11** complex promotes repair of DNA double-strand breaks (DSBs). Xenopus **Mre11** (X-**Mre11**) has been cloned, and its role in DNA replication and DNA damage checkpoint studied in cell-free extracts. DSBs stimulate the phosphorylation and 3'-5' exonuclease activity of X-**Mre11** complex. This induced phosphorylation is ATM independent. Phosphorylated X-**Mre11** is found associated with replicating nuclei. X-**Mre11** complex is required to yield normal DNA replication products. Genomic DNA replicated in extracts immunodepleted of X-**Mre11** complex accumulates DSBs as demonstrated by TUNEL **assay** and reactivity to phosphorylated histone H2AX antibodies. In contrast, the ATM-dependent DNA damage checkpoint that blocks DNA replication initiation is X-**Mre11** independent. These results strongly suggest that the function of X-**Mre11** complex is to repair DSBs that arise during normal DNA replication, thus unraveling a critical link between recombination-dependent repair and DNA replication.

=>